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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,311	06/25/2001	Marta Blumenfeld	G-046US02PCT	2795

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EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,311	BLUMENFELD ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-63* is/are pending in the application.

4a) Of the above claim(s) *57 and 60-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-56 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 42-56 and 59 and specifically biallelic marker 9494 of SEQ ID NO: 1 in the response filed April 24, 2003 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 42-56 and 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated nucleic acids consisting of SEQ ID NO: 1 or 2, isolated nucleic acids comprising SEQ ID NO: 3 or 4, and isolated nucleic acids consisting of at least 12 nucleotides of any one of SEQ ID NO: 1-4, does not reasonably provide enablement for nucleic acids comprising SEQ ID NO: 1 or 2, nucleic acids comprising or consisting essentially of 12 contiguous nucleotides of SEQ ID NO: 1-4 or nucleic acids having a "G" at nucleotide position 9494 of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are drawn to polynucleotides comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-4; polynucleotides consisting essentially of a contiguous span of at least 12 nucleotides of SQ ID NO: 1 and 2, wherein the span includes any TBC-1 biallelic marker; polynucleotides consisting essentially of a contiguous span of 8 to 50 nucleotides of SEQ ID NO: 1 or 2 wherein the 3' end of the contiguous span is located 3' upstream within 20 nucleotides of a TBC-1 biallelic marker; ; polynucleotides comprising a nucleotide sequence encoding at least 6 amino acids of SEQ ID NO: 5; and methods of making a TBC-1 polypeptide encoded by a nucleic acid comprising SEQ ID NO: 1-4.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification teaches a human genomic DNA sequence which has been set forth in the specification in 2 fragments: the first fragment is set forth in SEQ ID NO: 1 and consists of a 5' untranslated regulatory region, exon 1, exon 1bis, and exon 2; and the second fragment is set forth in SEQ ID NO: 2 and consists of exons A, B, C, D, E, F, G, H, I, J,

K, and L and 3' regulatory sequences. The specification also teaches that 2 alternate splice forms of the human nucleic acid sequence. The first splice form is represented by the cDNA of SEQ ID NO: 3, which consists of a 5' untranslated sequence, exons 1, 2, A, B, C, D, E, F, G, H, I, J, K, and L and a 3' regulatory sequence starting at position 3726. The second splice form is represented by the cDNA of SEQ ID NO: 4, which consists of a 5' untranslated sequence from nucleotides 1 to 175, exons 1bis, 2, A, B, C, D, E, F, G, H, I, J, K, and L and a 3' regulatory sequence. The specification teaches that the human genomic and cDNA sequences share sequence identity with the mouse TBC-1 gene. The mouse TBC-1 gene is set forth, for example, in U.S. Patent 5,700,927 and has been found to be associated with the differentiation of specific types of hematopoietic cells. The specification (see, for example, page 18) also teaches that the human TBC-1 nucleic acid is present in a region of chromosome 4 that has been linked to the occurrence of prostate cancer. Based on this information, the specification (page 6) states that the human TBC-1 gene "is potentially involved in the regulation of the differentiation of various cell types in mammals. A deregulation or an alteration of TBC-1 expression, or alternatively an alteration in the amino acid sequence of the TBC-1 protein may be involved in the generation of a pathological state related to cell differentiation in a patient, more particularly to abnormal cell proliferation leading to cancer states, such as prostate cancer." With respect to biallelic variants, the specification teaches a polymorphism which occurs in intron 1 at position 9494 of SEQ ID NO: 1. Eighteen additional polymorphisms were identified in introns A, B, D, G, H, I and J of the TCB-1 nucleic acid of SEQ ID NO: 2. The specification does not teach any specific functional properties associated with these particular polymorphisms. However, the specification (page 18) postulates that alterations in the

expression of TBC-1 may lead to an altered biological activity which may directly or indirectly cause cell proliferative disorders and diseases associated with abnormal cell proliferation, such as cancer.

The claims as broadly written include a genus of TBC-1 nucleic acids and fragments thereof which are not adequately taught in the specification and for which the specification has not provided sufficient guidance to enable the skilled artisan to use without undue experimentation. The claims encompass nucleic acids which are defined only in terms of the fact that they comprise SEQ ID NO: 1 or 2. These nucleic acids are not defined in terms of their functional properties and the flanking sequences are not defined. With respect to SEQ ID NO: 1, such claims include molecules in which only exon 1, exon 1bis and exon 2 are defined, and the remaining 3' nucleotides are undefined. With respect to SEQ ID NO: 2, such claims include molecules in which the exon, intron and 5' untranslated sequences are not defined. The claims further include nucleic acid consisting essentially of 12 contiguous nucleotides of SEQ ID NO: 1-4. These nucleic acids read on full length molecules in which only 12 nucleotides have been defined and the structure of the remaining nucleotides and function of the molecule is not characterized. The specification makes clear that the claims are intended to encompass all variants of the TBC-1. While the specification at page 30 states that the invention is intended to exclude the murine TBC-1 protein set forth in US Patent 5,700,927, the claims include nucleic acids encoding all homologs, splice variants, mutants and polymorphic variants of TBC-1 having similar or distinct functional properties. The disclosure of one splice variant and 19 polymorphic variants is not representative of the broadly claimed genus. The specification does not provide sufficient guidance as to what nucleotides may be added to the 3' or 5' terminus of

SEQ ID NO: 1 or 2 or 12 mers of SEQ ID NO: 1-4 which will result in a nucleic acid molecule that one of skill in the art could use without undue experimentation. The disclosure of one splice variant in one organism does not provide sufficient information to lead one to make and use additional splice variants from humans or other species without undue experimentation. While the specification does identify 19 polymorphisms, the TCB-1 genomic DNA spans 18,363 nucleotides and encompasses 14-15 exons. However, polymorphisms have been identified only in 8 introns. This does not constitute a representative number of the polymorphisms that may exist in each of the introns, exons and 5' and 3' untranslated sequences of the human and non-human TBC-1 genes. Additionally, the specification does not disclose any mutations in the TBC-1 gene and specifically does not disclose any mutations associated with the occurrence of proliferative diseases as is encompassed by the claims in view of the teachings in the specification. Accordingly, the specification has not taught a representative number of biallelic markers. Extensive experimentation would be required to identify additional markers to meet the broad scope of the claims because this would require extensive experiments of isolating and sequencing numerous additional genomic clones from a representative number of species and identifying polymorphisms which are present in the TBC-1 genes of these species at a frequency of at least 1%.

Furthermore, the specification does not provide adequate guidance as to how to use the biallelic markers. The specification has postulated that these markers may be associated with deregulating or altering the expression of TBC-1 and may be associated with the occurrence of proliferative disorders. However, the specification has not established that any of these polymorphisms are in fact involved in regulating or alerting the expression of TBC-1 or is

associated with the occurrence of a cell proliferative disorder. Extensive experimentation would be required to determine which if any of the disclosed polymorphisms are associated with regulation or expression of TBC-1 and with any particular proliferative cell disorder. In the absence of evidence of an association between the structural and functional properties a nucleic acid, it is highly unpredictable as to how the presence of a polymorphism in a coding or non-coding sequence will alter the expression of a nucleic acid or the activity of an encoded protein.

In view of the lack of guidance provided in the specification and the lack of information provided regarding additional TBC-1 homologs, splice variants, mutants and polymorphic variants, undue experimentation would be required to make and use the invention as it is broadly claimed.

3. Claims 42-56 and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polynucleotides comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-4; polynucleotides consisting essentially of a contiguous span of at least 12 nucleotides of SQ ID NO: 1 and 2, wherein the span includes any TBC-1 biallelic marker; polynucleotides consisting essentially of a contiguous span of 8 to 50 nucleotides of SEQ ID NO: 1 or 2 wherein the 3' end of the contiguous span is located 3' upstream within 20 nucleotides of a TBC-1 biallelic marker; polynucleotides comprising a

nucleotide sequence encoding at least 6 amino acids of SEQ ID NO: 5; and methods of making a TBC-1 polypeptide encoded by a nucleic acid comprising SEQ ID NO: 1-4.

The specification teaches a human genomic DNA sequence comprising a first fragment which is set forth in SEQ ID NO: 1 and consists of a 5' untranslated regulatory region, exon 1, exon 1bis, and exon 2; and a second fragment which is set forth in SEQ ID NO: 2 and consists of exons A, B, C, D, E, F, G, H, I, J, K, and L and 3' regulatory sequences. Two alternate splice forms of this nucleic acid sequence are also taught. The first splice form is represented by the cDNA of SEQ ID NO: 3, which consists of a 5' untranslated sequence, exons 1, 2, A, B, C, D, E, F, G, H, I, J, K, and L and a 3' regulatory sequence starting at position 3726. The second splice form is represented by the cDNA of SEQ ID NO: 4, which consists of a 5' untranslated sequence from nucleotides 1 to 175, exons 1bis, 2, A, B, C, D, E, F, G, H, I, J, K, and L and a 3' regulatory sequence. The specification teaches that the human genomic and cDNA sequences share sequence identity with the mouse TBC-1 gene. The mouse TBC-1 gene is set forth, for example, in U.S. Patent 5,700,927 and has been found to be associated with the differentiation of specific types of hematopoietic cells. The specification (see, for example, page 18) also teaches that the human TBC-1 nucleic acid is present in a region of chromosome 4 that has been linked to the occurrence of prostate cancer. Based on this information, the specification (page 6) states that the human TBC-1 gene "is potentially involved in the regulation of the differentiation of various cell types in mammals. A deregulation or an alteration of TBC-1 expression, or alternatively an alteration in the amino acid sequence of the TBC-1 protein may be involved in the generation of a pathological state related to cell differentiation in a patient, more particularly to abnormal cell proliferation leading to cancer states, such as prostate cancer." With respect to

biallelic variants, the specification teaches a polymorphism which occurs in intron 1 at position 9494 of SEQ ID NO: 1. Eighteen additional polymorphisms were identified in introns A, B, D, G, H, I and J of the TCB-1 nucleic acid of SEQ ID NO: 2. The specification does not teach any specific functional properties associated with these particular polymorphisms. The specification (page 18) postulates that alterations in the expression of TBC-1 may lead to an altered biological activity which may directly or indirectly cause cell proliferative disorders and diseases associated with abnormal cell proliferation, such as cancer.

The claims as broadly written do not meet the written description requirements of 35 U.S.C. 112, first paragraph, because the specification does not disclose and fully characterize the genus of any homolog, splice variant, biallelic variant or mutant form of TBC-1. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' requires a precise

definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the prior art teaches one TBC-1 cDNA and the specification teaches 2 splice forms of the human TBC-1 genomic and cDNA as well as 19 polymorphisms in the introns of the TBC-1 gene. This does not constitute a representative number of members encompassed by the genus of any nucleic acid comprising 12 nucleotides of SEQ ID NO: 1-4 or comprising SEQ ID NO: 1 or 2, wherein the flanking nucleotides and the functional activity of the nucleic acid are not defined and/or wherein the nucleic acid comprises or terminates 3' of a "TBC-1-related marker." It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g., in terms of functional activity, or in terms of being in linkage disequilibrium with other well characterized polymorphisms, etc). In the instant case, no such identifying characteristics have been provided for any additional polymorphisms. The broadest reasonable interpretation of the claims indicates that the claims are inclusive of a huge genus of biallelic markers present at any position in any TBC-1 gene, including the 3' and 5' untranslated regions, exon and intron regions of the TBC-1 genes, splice variants and mutant forms of TBC-1. While one could contemplate a nucleotide substitution at each and every position in the TBC-1 gene, such substitutions are not considered to be equivalent to specific polymorphisms associated with TBC-1 regulation or expression or associated with cell proliferative disorders. Rather, polymorphisms and mutations in the associated with TBC-1 regulation and expression and with the occurrence of specific diseases

represent a distinct group of nucleotide variations which are expected to occur at only specific locations within the gene and consist of specific nucleotide alterations. Accordingly, knowledge of the sequence of the wild-type TBC-1 gene does not allow the skilled artisan to envision all of the contemplated polymorphisms, mutations, splice variants and homologs encompassed by the claimed genus. Therefore, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 43-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 43-56 are indefinite over the recitation of "TBC-1 related biallelic marker" because it is not clear as to what is intended to be meant by this phrase. This phrase is not defined and the specification and it is not clear as to what is encompassed by a gene related marker. For example, it is unclear as to whether this is intended to refer to only TBC-1 genes or to any gene related in some unstated manner to a TBC-1 gene or to a marker in linkage disequilibrium to a TBC-1 gene or marker. Furthermore, with respect to claims 43, and 45-56, it is unclear as to what is intended to be encompassed by the biallelic marker. This marker is not

defined in terms of any particular structure or position within the TBC-1 gene and thereby one of skill in the art cannot determine what would be included by the biallelic marker.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claim 50 is rejected under 35 U.S.C. 102(b) as being anticipated by Zon et al (U.S. Patent No. 5,700,927).

Zon et al (see Figure 1 therein) discloses isolated TBC-1 nucleic acids which encode for a protein that contains at least 6 amino acids of present SEQ ID NO: 5 (see Applicants own alignment set forth in Figure 1 of the specification). It is noted that the specification states that the murine TBC-1 polypeptides taught by Zon are explicitly excluded from the claimed invention. However, this statement was made with respect to only polypeptides and not to polynucleotides. Furthermore, the claims as broadly written encompass the mouse TBC-1 polynucleotides and thereby are anticipated by the teachings of Zon.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306 or (703)-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers
July 21, 2003

CARLA J. MYERS
PRIMARY EXAMINER